Scarless Fetal Wound Healing: A Basic Science Review

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Summary: Scar formation is a major medical problem that can have devastating consequences for patients. The adverse physiological and psychological effects of scars are broad, and there are currently no reliable treatments to prevent scarring. In contrast to adult wounds, early gestation fetal skin wounds repair rapidly and in the absence of scar formation. Despite extensive investigation, the exact mechanisms of scarless fetal wound healing remain largely unknown. For some time, it has been known that significant differences exist among the extracellular matrix, inflammatory response, cellular mediators, and gene expression profiles of fetal and postnatal wounds. These differences may have important implications in scarless wound repair. (*Plast. Reconstr. Surg.* 126: 1172, 2010.)

A cutaneous scar is a macroscopic fibrous disturbance in the normal tissue architecture. Scarring occurs in the setting of both surgical and traumatic wounds, and is the normal outcome of the wound-healing process. The skin is the most frequently injured tissue, and dermal scarring can result in loss of function, movement restriction, and disfigurement.

Wound healing is a complex and tightly regulated process. Scarring involves regulated collagen deposition in response to tissue injury. The mechanism of scar formation involves inflammation, fibroplasia, formation of granulation tissue, and scar maturation. In response to tissue injury, inflammatory cells are recruited to sites of wounded tissue. The acute inflammatory response is followed by the proliferation of fibroblasts, which are cells responsible for synthesizing various tissue components, including collagen and fibrin. During the acute inflammatory phase, circulating progenitor cells migrate to injured tissue. Rapid cellular proliferation occurs, which ultimately results in the formation of new blood vessels and epithelium. Fibroblasts then differentiate into myofibroblasts, which are the cells responsible for collagen deposition and wound contraction. Scar formation ultimately results from excess accumulation of an unorganized extracellular matrix. Although scar remodeling occurs for months to years after the initial injury, complete restoration of the normal extracellular matrix architecture is never achieved.[1] Mature scars restore only 70 percent of the tensile strength of normal skin, and prescar function is never completely recovered.[2] Thus, wound healing is a fibroproliferative response that results in an incomplete regeneration of the original tissue and excessive production of an unorganized collagen meshwork (scar tissue).

In contrast to adult wound healing, the early gestation fetus has the remarkable ability to heal skin wounds without scar. This observation was first reported more than three decades ago[3] and has subsequently been confirmed in both animal models and human fetuses.[4] Since that time, an intensive research effort has focused on unraveling the mechanisms underlying scarless fetal wound repair (Table 1).

SCARLESS FETAL WOUND PHENOTYPE

Fetal Skin

The structure and histology of fetal skin changes dramatically with development. In the human embryo, a primitive epidermis first appears at gestational day 20. During weeks 4 to 8 of gestation, the primitive epidermis develops into a two-layered periderm and basal cell layer. The fetal epidermis begins to stratify at week 9, and ke-

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Table 1. Adult versus Fetal Wound Healing

	Adult Wound Healing	Fetal Wound Healing
Collagen content	Predominance of type I collagen provides strength and rigidity, but impedes cellular migration and regeneration	Predominance of type III collagen is optimal for cellular migration and proliferation
Hyaluronic acid	Low levels of hyaluronic acid inhibit cellular movement	High levels of hyaluronic acid facilitates cellular movement and traps water
Extracellular matrix modulators	Low matrix metalloproteinase to tissue-derived inhibitor ratio favors accumulation of collagen	High matrix metalloproteinase to tissue-derived inhibitor ratio favors extracellular matrix modulators turnover and remodeling
Adhesion proteins	Diminished up-regulation of adhesion proteins results in slower fibroblast migration	Rapid up-regulation stimulates cell attachment and migration
Platelets	Release platelet-derived growth factor, TGF-β1, and TGF-β2	Decreased degranulation and aggregation
Inflammatory cells	Many	Few
Interleukins	Rapid increase in proinflammatory cytokines, such as interleukin-6 and interleukin-8	Increased expression of the anti-inflammatory cytokine interleukin-10, which decreases production of interleukin-6 and interleukin-8
TGF-β	High levels of TGF-β1 and TGF-β2	Low levels of TGF-β1 and TGF-β2; increased TGF-β3
Gene expression	Delayed up-regulation of genes involved in cell growth and proliferation	Rapid up-regulation of genes involved in cell growth and proliferation
Progenitor cells	Skin progenitor cells found at inadequate numbers to mediate scarless repair	Skin progenitor cells migrate to sites of injury and mediate scarless repair

TGF, transforming growth factor.

ratinization begins at week 14. By week 16, the fetal epidermis has many of the components of the adult epidermis: a basal cell layer, an intermediate layer, hair follicles, sweat glands, and follicular keratinization. After 24 weeks of gestation, fetal skin development is characterized by rapid growth and maturation, and at birth the neonatal skin is histologically indistinguishable from adult skin (Fig. 1).[5–7]

Fetal Cutaneous Wound Healing

Scarless wound healing has been observed in the fetuses of mice, rats, pigs, monkeys, and humans.[8] In fetal mammals, the ability to repair wounds scarlessly is age-dependent.[9,10] In other words, fetal skin heals scarlessly before a certain gestational age, after which point typical scar formation occurs. In humans, scarring of wounds begins at approximately 24 weeks of gestation, whereas in mice scarring of wounds begins on embryonic day 18.5 (average gestation period for mice is 20 days).[11–13] This transition point, however, is modulated by wound size. For example, as wound size increases in fetal lambs, the ability to heal scarlessly is lost earlier during gestation.[9]

In response to tissue injury, the fetal dermis has the ability to regenerate a nondisrupted collagen matrix that is identical to that of the original

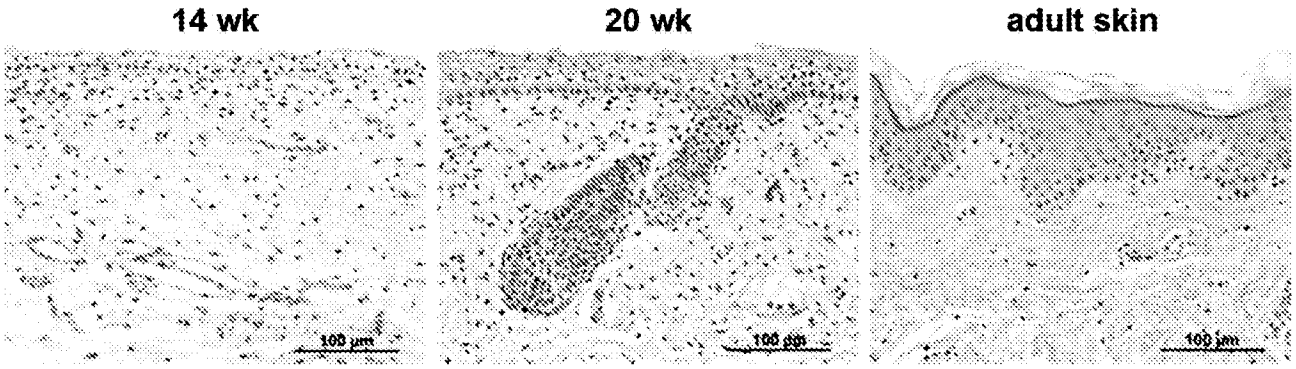

Fig. 1. Histology of human fetal skin at 14 and 20 weeks of gestation and adult skin. (*Left*) At 14 weeks, the epidermis consists of a basal layer, an intermediate cell layer, and a periderm. (*Center*) At 20 weeks, the number of intermediate cell layers has increased, and developing hair follicles are visible. (*Right*) Adult skin has a less cellular dermis and a multilayered epidermis with basal, spinous, granular, and cornified layers. *Scale bars* = 100 μm. Reproduced with permission from Springer from Coolen NA, Schouten KC, Middelkoop E, et al. Comparison between human fetal and adult skin. *Arch Dermatol Res.* 2010;302:47–55.

tissue.[14–16] In addition, dermal structures, such as sebaceous glands and hair follicles, form normally after fetal injury (Fig. 2).[17] Although the exact mechanisms of scarless fetal wound healing are still unknown, they are thought to be due to differences between the extracellular matrix, inflammatory response, cellular mediators, differential gene expression, and stem cell function in fetal and postnatal wounds.[18–26]

Scarless Repair Is Intrinsic to Fetal Skin

The capacity for scarless repair was initially attributed to the sterile intrauterine environment. Amniotic fluid is rich in hyaluronic acid and growth factors but devoid of bacteria and inflammatory stimulators; thus, it was thought to be an environment conducive to scarless wound repair. Early studies, however, demonstrated that the intrauterine environment is neither necessary nor sufficient for scarless repair (Table 2). For example, fetal marsupials develop outside the uterus in a maternal pouch and yet heal cutaneous wounds scarlessly.[27] Experiments have also shown that adult sheep skin transplanted onto the backs of fetal sheep, bathed in the amniotic fluid of the intrauterine environment, heal incisional wounds with scar while adjacent wounds in fetal skin heal scarlessly.[28] In addition, human fetal skin heals without scar when it is transplanted into the subcutaneous tissue of adult athymic mice.[29]

FETAL EXTRACELLULAR MATRIX

The extracellular matrix plays an important role in cell adhesion, differentiation, and proliferation. This matrix is a dynamic layer of collagen, glycos-

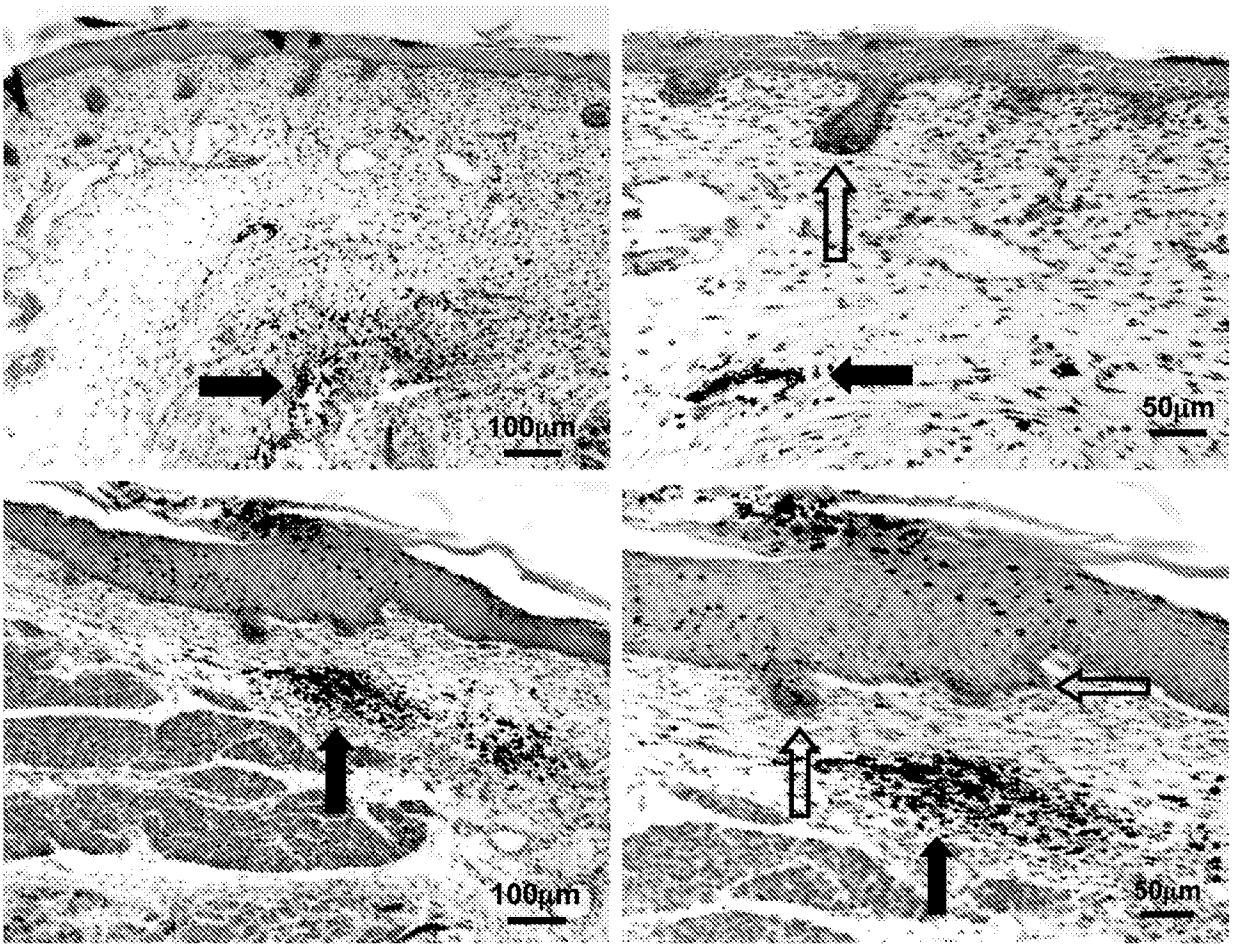

Fig. 2. Scarless healing of E16 fetal mouse wounds (hematoxylin and eosin stain). *Black arrows* indicate the India ink tattoo made at the time of wounding to demonstrate scarless wound location. Healed wounds (*above, left* and *below, left*) at 72 hours (100×). The epidermal appendage (developing hair follicles) pattern shows numerous appendages directly in the healed wound. Magnified views of the same wounds (*above, right* and *below, right*) showing epidermal appendages (*open arrows*) within the wound site (200×). No inflammatory infiltrate is present. Reproduced from Beanes SR, Hu FY, Soo C, et al. Confocal microscopic analysis of scarless repair in the fetal rat: Defining the transition. *Plast Reconstr Surg.* 2002;109:160–170.

Table 2. Factors Influencing Fetal Wound Healing

Modifying Factors	Examples
Tissue specificity	Skin heals scarlessly; gastric, intestinal, and diaphragmatic tissue heals with scar
Wound size	Larger wounds are more likely to heal with scar; in fetal lambs, over 50% of wounds >4 mm in diameter heal with scar
Species specificity	Wounds heal scarlessly in fetal mice, rats, pigs, monkeys, and humans; excisional wounds in fetal sheep contract and heal; excisional wounds in fetal rabbits do not heal but continue to enlarge as the fetus grows
Gestational age	Ability to heal wounds scarlessly is age dependent; the probability of scar formation increases with increasing gestational age

aminoglycans, proteoglycans, and adhesion proteins that undergoes a series of changes before reaching its adult phenotype.[18–20,22] The fetal extracellular matrix is optimized to facilitate cellular migration and proliferation, which may have important implications in wound healing. Thus, the fetal extracellular matrix may provide an environment that is conducive toward scarless wound repair.

Collagen Content

There are phenotypic differences between the collagen content and cross-linking patterns in fetal and postnatal wounds. In fetal wounds, type III collagen is rapidly deposited in a fine reticular network that is indistinguishable from uninjured skin (Fig. 3).[16] Postnatally, the ratio of type I to type III collagen in wounds increases.[30] The predominance of type I collagen in postnatal wounds provides regenerating tissue with more strength and rigidity, but may impede cellular migration and regeneration. Early scar formation in late gestation fetal wounds demonstrates larger collagen fibers with greater interfiber space (Fig. 4).[16]

Hyaluronic Acid

Hyaluronic acid is a glycosaminoglycan that is one of the chief components of the extracellular matrix. The net negative charge of hyaluronic acid traps and impedes water molecules, which allows resistance to deformation and facilitates cellular movement.[31] In general, fetal skin contains more hyaluronic acid than adult skin, and fetal fibroblasts express more hyaluronic acid receptors.[32,33] In scarless fetal wounds, the hyaluronic acid content of the extracellular matrix is increased more rapidly than in adult wounds. Fetal wounds also have fewer proinflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha, that act to down-regulate hyaluronic acid expression.[34] Because fetal skin contains more hyaluronic acid than adult skin, several investigators have proposed a role of hyaluronic acid in scarless healing.[35,36]

Proteoglycan Extracellular Matrix Modulators

Proteoglycan extracellular matrix modulators regulate collagen synthesis, organization, and degradation. Levels of decorin, a modulator of collagen fibrillogenesis, are up-regulated in adult wounds.[18] Conversely, levels of fibromodulin, another modulator of collagen fibrillogenesis, are lower in adult wounds.[21] Fibromodulin inactivates transforming growth factor (TGF)-beta, a key cytokine involved in wound healing, and has been shown to have an antiscarring effect during wound repair.[21] Lysyl oxidase expression is increased in adult wounds, and this modulator has been implicated in the pathogenesis of some fibrotic diseases.[19]

Matrix metalloproteinases and tissue-derived inhibitors are involved in extracellular matrix turnover. Scarless fetal wounds have a higher ratio of metalloproteinase to tissue-derived inhibitor expression, which favors remodeling over accumulation of collagen.[37]

Adhesion Proteins

Scarless fetal wounds have an enhanced ability to up-regulate extracellular matrix adhesion proteins, such as tenascin and fibronectin.[38–40] These adhesion proteins mediate cellular attachment to the extracellular matrix and attract fibroblasts, keritinocytes, and endothelial cells to sites of injury.[41] During development, tenascin facilitates cell movement and fibronectin facilitates cell anchoring. Early gestation fetal rabbit wounds express fibronectin 4 hours after wounding, whereas fibronectin expression is not seen until 12 hours after wounding in the adult.[42] Similarly, tenascin appeared at 1 hour in the wounded fetus, 12 hours in the wounded neonate, and at 24 hours after wounding in the adult mouse.[40] The rapid deposition of tenascin in fetal wounds may stimulate early cell migration, whereas the large amounts of fibronectin may stimulate cell attachment and wound repair. These factors, taken together, may promote rapid deposition of an organized matrix that has less scarring.

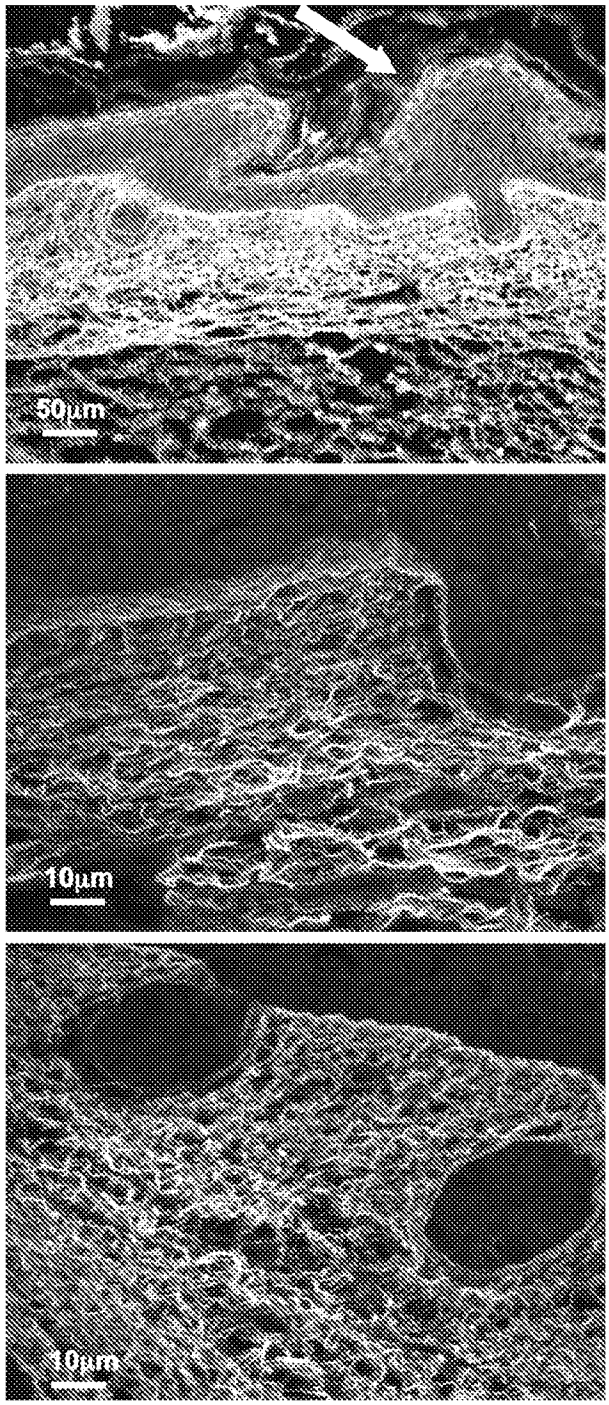

Fig. 3. Scarless healing of E16 fetal rat wounds (confocal microscopy). Collagen fibers are stained with sirius red and appear white. (*Above*) Healed wound harvested at 72 hours (200×). The epidermis is thickened at the wound site (*arrow*). The collagen fiber is reticular and unchanged from the surrounding dermis. (*Center*) Healed wound harvested at 72 hours under a higher magnification (1000 ×). The collagen fibers are thin and closely approximating each other with little interfiber space. The fibers are arranged in a wispy reticular pattern. (*Below*) Nonwounded E19 skin at the same magnification as B (1000×). The dermal collagen fiber pattern is identical to the center image.

MEDIATORS OF SCARLESS REPAIR

Inflammatory Cells

Fetal wounds heal rapidly with a paucity of inflammation. This observation has stimulated interest in the role of cellular inflammatory mediators, cytokines, and growth factors in fetal wound healing. In the postnatal animal, disruption of tissue integrity stimulates platelet activation, cytokine production, and chemotaxis of macrophages and neutrophils.[43] Scarless wounds, however, are characterized by a relative lack of inflammation.[41] Furthermore, introduction of inflammation into normally scarless wounds produces dose-dependent increases in wound macrophages, neutrophils, collagen deposition, and scarring.[23] Conversely, reduction of inflammation in postnatal wounds also reduces scarring.[44] This suggests an important role of inflammation in scar formation.

Platelets

The absence of an acute inflammatory infiltrate in scarless wounds may be partly explained by decreased fetal platelet degranulation and aggregation. Although there is no difference in size, organization, or granule content by transition electron microscopy in fetal compared with adult platelets, fetal platelets produce less platelet-derived growth factor, TGF-β1, and TGF-β2 than their adult counterparts.[45] The proinflammatory signals that are released from the platelet plug are responsible for mediating the early phase of the wound healing process. Although exposure of fetal platelets to collagen in vitro does stimulate growth factor release, the capacity for fetal platelet aggregation is age-dependent.[46] Early gestation fetal platelets do not aggregate, whereas late gestation fetal platelets aggregate just as effectively as adult platelets. The transition point for this platelet response corresponds to the transition point from scarless to scarring repair. Thus, the reduced function of early gestation fetal platelets may be one mechanism of scarless repair.

Neutrophils

Neutrophils neutralize and engulf bacteria. Cytokines TGF-β1 and platelet-derived growth factor recruit neutrophils to the site of injury. In turn, neutrophils release self-stimulating cytokines and chemoattractants for fibroblasts and macrophages.[43]

Reproduced from Beanes SR, Hu FY, Soo C, et al. Confocal microscopic analysis of scarless repair in the fetal rat: Defining the transition. *Plast Reconstr Surg.* 2002;109:160–170.

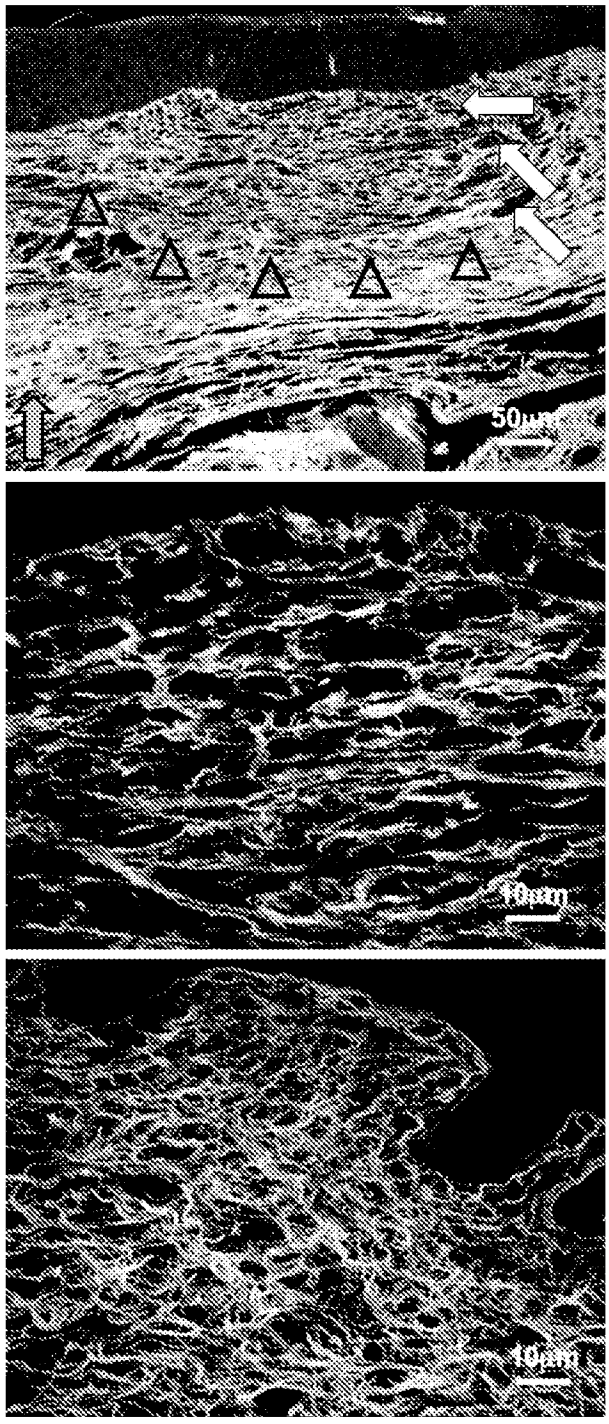

Fig. 4. Early scar formation after the transition point in E18 fetal rat wounds (confocal microscopy). Collagen fibers are stained with sirius red and appear white. (*Above*) Healed wound at 72 hours (200×). The wound dermal collagen pattern (*open triangles*) is different from the surrounding nonwounded dermis (*green arrow*). The fibers are less densely compacted. No epidermal appendages are present. Neovascularization is shown with the *white arrows*. (*Center*) Healed wound at 72 hours at a higher magnification (1000×). The collagen fibers are thicker but with greater interfiber spaces compared with nonwounded dermis. (*Below*) Nonwounded skin at E21 days gestational age (1000 ×). When compared with wound collagen fibers (*center*), nonwounded dermal collagen fibers are thinner with less interfiber space. Reproduced from Beanes SR, Hu FY, Soo C, et al. Confocal microscopic analysis of scarless repair in the fetal rat: Defining the transition. *Plast Reconstr Surg.* 2002;109:160–170.

Fewer neutrophils are present in the fetal wound, and an age-dependent defect in the ability of fetal neutrophils to phagocytose pathogenic bacteria has been demonstrated in fetal sheep.[47]

Fibroblasts

Synthesis and remodeling of the extracellular matrix by fibroblasts is essential for wound healing. Adult and fetal fibroblasts reside locally in the injured tissue or are recruited to the site of injury by soluble chemoattractants released by macrophages and neutrophils.[48] Fetal wounds characteristically have less inflammatory cells and cytokine expression, yet heal more rapidly than adult wounds. This may be partly explained by intrinsic differences between adult and fetal fibroblasts.

Fetal and adult fibroblasts display differences in synthetic function of collagen, hyaluronic acid, and other extracellular matrix components. In vitro, fetal fibroblasts synthesize more type III and IV collagens than their adult counterparts, correlating with an increase in prolyl hydrolase activity, the rate-limiting step in collagen synthesis.[49,50] Collagen synthesis is delayed in the adult wound while fibroblasts proliferate. In contrast, fetal fibroblasts simultaneously proliferate and synthesize collagen.[48]

Fetal fibroblasts have more surface receptors for hyaluronic acid, which also serves to enhance fibroblast migration.[51] In addition, TGF-β, which inhibits migration of confluent fibroblasts in vitro, is decreased in the fetal wound.[52]

Differences in contractile fibroblasts, termed "myofibroblasts," have also been reported. Myofibroblasts, detected by the presence of alpha-smooth muscle actin appear in the adult wound 1 week after wounding. The content of myofibroblasts is greatest during the second and third week and then decreases with time,[48] whereas wounds made early in gestation have virtually no myofibroblasts. In contrast, scarring fetal and postnatal wounds have progressively more active myofibroblasts, which correlates with contraction and degree of scarring.[53] Overall, the fetal fibroblast has an intrinsic ability to synthesize a dermal extracellular matrix that is superior to the adult fibroblast in terms of its ability to generate an organized dermis at sites of injury.

Cytokines

TGF-β

Since shortly after its discovery more than 20 years ago, TGF-β was shown to be involved in wound healing. The TGF-β isoforms are involved in all steps of the wound repair process and have divergent effects on scar formation and wound healing. The expression of TGF-β1 and TGF-β2 is increased in adult wounds, whereas it is unchanged in fetal wounds.[54] Scarless wounds in fetal mice have less TGF-β1 than neonatal or adult wounds.[55] Insertion of polyvinyl alcohol sponges containing TGF-β1 into fetal wounds leads to scar formation.[55] Similarly, treatment of adult rat wounds with neutralizing antibodies to TGF-β1 and TGF-β2 reduces scar formation.[54,56]

Furthermore, the relative proportion of TGF-β isoforms, and not the absolute amount of any one isoform, may determine the wound phenotype. In scarless fetal wounds, TGF-β3 expression is increased while TGF-β1 expression is unchanged. Conversely, TGF-β1 expression is increased and TGF-β3 expression is decreased in scarring fetal wounds.[57] Treatment of adult wounds with exogenous TGF-β3 reduces scar formation.[58] This suggests the ratio of TGF-β3 to TGF-β1 may determine whether tissue regenerates with or without scar formation.

Interleukins

Interleukins are cytokines important in chemotaxis and activation of inflammatory cell mediators. Interleukin-6 stimulates monocyte chemotaxis and macrophage activation, whereas interleukin-8 attracts neutrophils and stimulates neovascularization.[59] Wounding stimulates a rapid increase in interleukin-6 and interleukin-8, which persists at 72 hours in the adult but disappears by 12 hours in the fetus.[59,60] Both interleukin-6 and interleukin-8 expression are significantly lower in early fetal fibroblasts compared with adult fibroblasts. The addition of interleukin-6 to fetal wounds produces scar in normally scarless wounds. Interleukin-10 has an anti-inflammatory function through decreased production of interleukin-6 and interleukin-8. Wounds in fetal skin grafts harvested from early gestation interleukin-10 knock-out mice and grafted onto syngeneic adult mice heal with significant inflammation and scar.[61] In an initial study, adult mouse wounds were treated with an interleukin-10 overexpression adenoviral vector. Inflammation was reduced, and scarless healing occurred.[62] This strategy will potentially have potential therapeutic implications for human adult wounds.

GENE EXPRESSION PROFILING IN FETAL AND ADULT WOUNDS

Genomic microarray analysis has shown that scarless fetal wounds and scarring postnatal wounds have different gene expression profiles.[63] In scarless fetal wound healing, there is rapid upregulation of groups of genes involved in cell growth and proliferation, which likely contributes to rapid wound closure in the fetus. These genes are important for DNA transcription, DNA repair, cell cycle regulation, protein homeostasis, and intracellular signaling. At early time points, the proportion of genes with increased expression is significantly higher in fetal wounds. By 24 hours, however, the postnatal wound transcriptome has more genes with increased expression compared with fetal wounds.[63] The rapidly changing gene expression profile in fetal wounds likely reflects the more rapid healing rate in the fetus.

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GLOSSARY OF TERMS

Basal cell layer: The deepest layer of the epidermis. The basal cell layer is a continuous layer of cells that is considered to be composed of epidermal stem cells.

Extracellular matrix: The extracellular protein and proteoglycan scaffold that provides structural support to cells and sequesters inactive growth factors.

Green fluorescent protein: A fluorescent marker frequently used in molecular biology.

Glycosaminoglycans: Long unbranched polysaccharides that represent an important component of connective tissue.

Hyaluronic acid: Anionic glycosaminoglycan widely distributed throughout connective and epithelial tissue, and represents one of the chief components of the extracellular matrix.

Interleukins: A group of proinflammatory and anti-inflammatory cytokines that represent an important part of the inflammatory response.

Myofibroblasts: Fibroblasts that have features characteristically associated with smooth muscle cells.

Proteoglycans: Proteins that contain carbohydrate molecules. These proteins are an important component of the cell membrane and extracellular matrix.

TGF-β: A growth factor that controls proliferation, cellular differentiation and other functions in cells.

TGF-α: A cytokine involved in systemic inflammation and is involved in the acute phase response.

Transcriptome: The set of all messenger RNA molecules produced in one population of cells.

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